PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Wilhelmus Everhardus Hennink, Cornelus Franciscus van Nostrum, and Silvia Johanna de Jong

Examiner: B. Fubara

Confirmation No.: 8024

Group Art Unit: 1615

Serial No.: 09/913,967

Docket: 313632001000

Filed: December 31, 2001

Dated: January 20, 2005

For: Stereocomplex hydrogels

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I hereby certify this correspondence is being deposited with the United States Postal Service as first class mail, postpaid in an envelope, addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450
on January 20, 2005

*Signature:*_____

DECLARATION UNDER 37 CFR 1.132

I Wilhelmus Everhardus Hennink of Zuidplaslaan 120 NL-2743 CZ Waddinxveen, the Netherlands declare as follows.

1. I am employed by the University of Utrecht as professor. I am an expert in the field of hydrogel compositions, as evidenced by the *curriculum vitae* attached hereto as Exhibit A. I am an inventor in the present application and am also a co-inventor in WO 98/00170

2. I have reviewed the Office Action mailed by the Examiner on October 20, 2004, and the references cited by the Examiner in the Office Action. This declaration is being submitted in response to the Office Action to distinguish the present invention from the prior art references.

3. In accordance with the invention, a hydrogel is formed by mixing aqueous solutions or dispersing of a water-soluble or dispersible polymer (e.g. dextran) to which oligomers of opposite chirality are grafted or otherwise substituted. By this process a physically linked hydrogel is obtained.
Stereocomplex formation between poly(D-lactic acid) and poly(L-lactic acid) has been demonstrated in the prior art to occur when these polymers are dissolved in a suitable organic solvent (e.g. dichloromethane) followed by evaporation of the solvent.
We were the first who demonstrated that stereocomplexes can be formed by mixing aqueous solutions/dispersions of a water-soluble or dispersible polymer (e.g. dextran) to which oligomers of opposite chirality are substituted (preferably grafted).

4. One of the important aspects distinguishing the subject-matter of present claims from the cited references of Okihara et al. (J. Macromol. Sci. Phys (1990) B30 (1 & 2) 119-140) and WO 98/00170 (in the name of the undersigned) is that the present claims relate to a hydrogel composition comprised of a mixture of two types of water soluble or water dispersible polymers that are substituted with oligomers or co-oligomers, wherein the (co-)oligomers in the first polymer are at least partly formed from chiral monomers and wherein the (co-)oligomers in the second polymer are at least partly formed from chiral monomers with a chirality that is opposite to that of said monomers in the first polymer, such that the chiral part of the (co-)oligomers are in essence complementary to that in the first polymer.

5. Okihara et al. does not disclose a hydrogel. Firstly, no water is present in the described system. Hence, it is impossible to have a hydrogel present.

6. Secondly, Okihara et al. does not disclose water soluble polymers. The Examiner states (on page 2 and also other pages) that "polymers of lactic acid and glycolic acid are water-soluble; at the worst they are sparingly soluble". This statement is incorrect. Poly(lactic acid) and its copolymers with glycolic acid are not soluble in water, but they only

dissolve in organic solvents. Confusingly, these polymers are sometimes called water-soluble in literature, but this characteristic refers to the ability of these polymers to degrade to low molecular weight degradation products when solid specimens of these polymers are placed in an aqueous solution. The degradation products may be water-soluble. The polymer itself is not. This degradation process takes from a few weeks to a years, depending on a great number of factors) (see e.g. Hennink WE, Van Steenis, JH and Van Nostrum CF. Fast degradable polymers. In: Reflexive Polymers and Hydrogels. In: Understanding and designing fast responsive polymeric system. Ed: Yui, N. Mrsny RJ, and Park K. CRC Press page 401-423, 2004). This alleged "water-solubility" is something completely different from the physico-chemical definition of solubility (i.e. the generally used definition).

7. Thirdly, Okihara et al. does not disclose polymers substituted with an oligomer. Okihara et al. discloses non-substituted homopolymers.

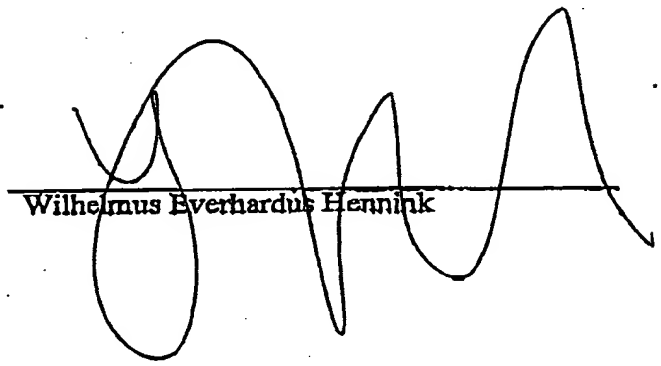
8. WO 98/00170 does not disclose a hydrogel comprising two different substituted polymers, wherein the chiral parts of the substituents are in essence complementary to each other either.

9. The only reference made to the isomeric form of the lactide is in Example 3, which describes the synthesis of dex-lactate-HEMA by coupling L-lactide and HEMA thereby forming HEMA-lactate, and coupoling the HEMA-lactate to dextran. In this example the lactate is used as a hydrolysable spacer and not as a chiral substituent of a water soluble polymer that interacts noncovalently with another polymer having a lactide substituent of opposite chirality. Thus, WO 98/00170 fails to describe a gel using two types of polymers, each having a chiral substituent that is complementary to the other. Furthermore, unlike the invention as claimed, the hydrogels in WO 98/00170 are prepared by free radical polymerization of a crosslinkable group such as methacrylate, acrylate, vinyl ethers and vinyl esters, resulting in the formation of covalent bonds.

10. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true. Further that these statements were made with the knowledge that willfully false statements, and the like, so made are punishable by fine or imprisonment or both under Section 1001 of Title 18

of the United States Code, and that such willfully false statements may jeopardize the validity of the application of any patent issued thereon.

Date: Jan 20th 2005

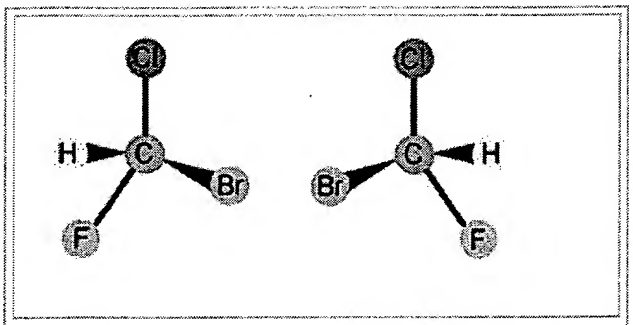


Wilhelmus Everhardus Hennink

Chirality (chemistry)

From Wikipedia, the free encyclopedia.

In chemistry, a molecule is **chiral** if it is not superimposable on its mirror image regardless of how it is contorted. Your hands are also chiral - mirror images of one another and non-superimposable - and chiral molecules are often described as being 'left handed' or 'right-handed'.



The two enantiomers of bromochlorofluoromethane

The study of chirality falls in the domain of stereochemistry. The two non-superimposable, mirror-image forms of chiral molecules are referred to as **enantiomers**. Chiral compounds exhibit optical activity, so enantiomers are also sometimes called optical isomers. The two enantiomers of such compounds may be classified as levorotary or dextrorotary depending on whether they rotate plane-polarised light in a left- or right-handed manner, respectively. A 50/50 mixture of the two enantiomers of a chiral compound is called a **racemic mixture** and does not exhibit optical activity. Chiral molecules are sometimes referred to as being "dissymmetric"; chirality and dissymmetry being one in the same.

In more technical terms, the symmetry of a molecule (or any other object) determines whether it is chiral or not. A molecule is achiral (that is, not chiral) if and only if it has an axis of improper rotation, that is, an n-fold rotation (rotation by 360°/n) followed by a reflection in the plane perpendicular to this axis which maps the molecule on to itself. Thus a molecule is chiral if and only if it lacks an improper rotation axis. They are not necessarily asymmetric (i.e. without symmetry), because they can have other types of symmetry, for example rotational symmetry. However, all naturally-occurring amino acids (except glycine) and many sugars are asymmetric as well as chiral. Chirality may also be defined in mathematical terms.

Chirality is of critical importance in chemistry and unites the traditionally-defined subdisciplines of inorganic chemistry, organic chemistry and physical chemistry. Many biologically-active molecules are chiral, including the naturally-occurring amino acids (the building blocks of proteins) and vitamins. Interestingly, these compounds are **homochiral**, that is **all** of the same chirality. The origin of homochirality in the biological world is the subject of vigorous debate. Many coordination compounds are also chiral, for example the well-known $[Ru(2,2'\text{-bipyridine})_3]^{2+}$ complex in which the bipyridine ligands adopt a propeller-like arrangement.

Enzymes, which themselves are always chiral, often distinguish between the two enantiomers of a chiral substrate. This can be visualised in everyday terms by imagining the enzymes to have three-dimensional glove shaped cavities which bind these substrates. If this "glove" is right-handed, then right-handed molecules will fit inside snugly and thus be bound tightly. On the other hand, left-handed molecules won't fit well - just like putting your left hand into a right-handed glove. Although this is an oversimplification of the recognition process (enzyme cavities are not really "glove shaped"), it is a useful illustration of a more general point: chiral objects have different interactions with the two enantiomers of other chiral objects.

Other biological processes may be triggered by only one of the two possible enantiomers of a chiral molecule, often being unresponsive to the other enantiomer. For example, S-carvone ("left-handed") is the flavor of caraway, while R-carvone ("right-handed") is the flavor of spearmint. Many chiral drugs must be made with high enantiomeric purity due to toxic activity of the 'wrong' enantiomer. An example of this is thalidomide which is racemic — that is, it contains both left and right handed isomers in equal amounts. One enantiomer is effective

against morning sickness, and the other is teratogenic. It should be noted that the enantiomers are converted to each other *in vivo*. That is, if a human is given D-thalidomide or L-thalidomide, both isomers can be found in the serum. Hence, administering only one enantiomer will not prevent the teratogenic effect in humans.

Most commonly, chiral molecules have **point chirality** which centers around a single asymmetric atom (usually a carbon atom). This is the case for chiral amino acids where the alpha carbon atom is the stereogenic centre, having point chirality. A molecule can have multiple chiral centers without being chiral overall if there is a symmetry element (mirror plane or inversion center) which relates those chiral centers. Such compounds are referred to as **meso** compounds. It is also possible for a molecule to be chiral without any specific chiral centers in the molecule. Examples include 1,1'-bi-2-naphthol (BINOL) and 1,3-dichloro-allene which have planar chirality or axial chirality. The $[Ru(2,2'\text{-bipyridine})_3]^{2+}$ complex above is an example of a chiral molecule that has high symmetry. It belongs to the symmetry point group D_3., meaning it has one three-fold rotational symmetry axis and three perpendicular two-fold axes. In this case, the Ru atom may be regarded as a stereogenic centre with the complex having point chirality.

One must make a clear distinction between **conformation** and **configuration** when discussing chirality in a molecular context. Conformations are temporary positions atoms in a molecule can assume as a result of bond rotation, bending, or stretching as long as no bonds are broken. Configurations are structures of a molecule which are assumed **not** to be interconvertible under ambient conditions. Enantiomers, and other optically active isomers such as diastereomers, are examples of configurational isomers.